P-17-0294 Respond to Submitter 2017-11-09 Comments Resp Sens 2018-03-28 FINAL

Date – March 28, 2018

MEMORANDUM

SUBJECT: P-17-0294 Respond to Submitter Comments on Respiratory Sensitization Hazard Determination

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THRU: Peer Reviewer
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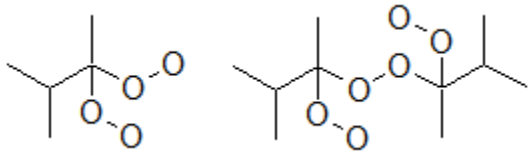
1 BACKGROUND

In an August 9, 2017 letter the submitter provided a number of arguments about the EPA concern for dermal and respiratory sensitization to the PMN. EPA responded in a September 9, 2017 memorandum. In a November 9, 2017 letter, the submitter provided rebuttal arguments to the EPA response. This memorandum addresses the new comments from the submitter.

1.1 Pre-FOCUS notes

PMN Structure:



2-Butanone, 3-methyl-, peroxide
CAS #: 182893-11-4

SAT Assessment:

- Absorption: Expect good absorption all routes (pchem and submitted studies).

- SAT Health Summary: Based on data submitted on the PMN there are concerns for irritation and corrosion to all exposed tissues, concerns for sensitization, and concerns for liver toxicity. Marginal concerns for mutagenicity and oncogenicity based on potential free radical formation.

PMN Data:

Data Submitted with PMN

- Sensitization guinea pig maximisation-test – positive

[redacted]

- In Vitro Mammalian Cell Gene Mutation Mouse Lymphoma Cells – [redacted]
- Acute Dermal Toxicity Rat –LD50 > [redacted]
- Primary Skin Irritation/Corrosion Rabbit – [redacted]
- 28 day Study Rat oral gavage (0, 3, 15 and 75 mg/kg/day). [redacted]

2 RESPONSE TO AKZONOBEL NOVEMBER 9 COMMENTS

The AkzoNobel comments were divided into an Executive Summary and Detailed Comments and Questions sections. The following addresses the comments in both sections.

2.1 Executive Summary

2.1.1 Comment 1

AkzoNobel Comment:

There is no validated method to test or predict a chemical's potential to cause respiratory sensitization. The only means to identify a human respiratory sensitizer is in a human using established medical criteria. The letter cites Holsapple, 2005; Arts, 2007; and Cochrane 2015 in support.

EPA Response:

Agree. EPA does not currently recognize a valid test in animals to predict human respiratory sensitization. However, it is currently the EPA policy to assume cross sensitization based on other reactive chemicals like isocyanates.

2.1.1 Comment 2

AkzoNobel Comment:

With respect to the relationship between skin sensitization and respiratory sensitization, the European Union technical staff has concluded, "it is important to note that in reality only a very few precedents for the elicitation of pulmonary reactions by skin sensitizing chemicals in humans have been observed, and in practice it may not represent a significant health issue" (ECHA, 2015).

EPA Response:

Disagree. The 2017 Version 6 of the ECHA document (ECHA, 2017) does not contain this statement. Page 315 states *"For substances that sensitise via the respiratory tract, there is still uncertainty regarding the exact mechanisms leading to respiratory sensitisation. Based on the current knowledge the induction of respiratory sensitisation can occur via inhalation or dermal exposure to the sensitising substance (Redlich, 2010; Kimber et al., 2015)."*

In addition lung sensitization can potentially lead to a fatal asthma attack.

[redacted]

2.1.1 Comment 3

AkzoNobel Comment:

In summary, we conclude there are no test data, scientific literature references, clinical testing, or occupational exposure records for the PMN substance or on structural peroxide analogs that would warrant the EPA concern. In addition, there do not appear to be any QSAR analyses available that would indicate the PMN substance is a respiratory sensitizer: there are no known data showing peroxides have caused respiratory sensitization that can be used in the training sets to develop such QSAR tools. And it should be stressed that existing sensitization QSAR model structural alerts not only do not include the peroxy functional group, but are based on chemical sensitizers, not specifically chemical respiratory sensitizers/asthmagens (ECHA, 2015).

EPA Response:

Disagree. See response to Comment 2. The lack of worker complaints does not preclude sensitization issues. The statement is not supported by a systematic epidemiology study, or worker surveillance.

2.1.2 Comment 4

AkzoNobel Comment:

We do not understand why EPA has recommended that self-contained breathing protection be used in the workplace. Existing engineering controls and PPE have been shown to provide adequate protection during 12 years of production and use of the PMN chemical in Europe and a similar, effective approach will be used in the U.S.

EPA Response:

In the absence data, EPA must regulate the PMN substance as we would other respiratory sensitizers, such as isocyanate. NIOSH recommends that MDI exposure be limited to 0.05 (mg/m3), so in the absence of data, EPA uses the NIOSH recommendation as the exposure level for respiratory sensitizers. Based on exposure models for this use, EPA expects exposures of higher than 0.05 (mg/m3). Therefore this use may present an unreasonable risk to human health if unmitigated by engineering controls that would reduce exposure to below the NIOSH recommendation or an air supplied respirator. EPA has recommended an air supplied breathing respirator in order to the potential for unreasonable risk during spray operations of respiratory sensitizers. This is in accordance with the NIOSH recommendation for MDI, "On the basis of these finding, NIOSH concludes that only a full-facepiece, supplied-air respirator provides the necessary protection during MDI spray operations".

2.1.3 Conclusions

2.1.3.1 Conclusion (1)

AkzoNobel Comment:

(1) there are no data on the PMN chemical that indicate it should be considered a respiratory sensitizer;

EPA Response:

Disagree. The PMN is positive in the Guinea Pig maximization test. As noted in ECHA (2017) above, a skin sensitizer has the potential to also induce respiratory sensitization. There is too much uncertainty in the PMN cross sensitization and its extreme corrosive action to conclude this chemical is safe without substantial PPE protection.

[redacted]

2.1.3.1 Conclusion (2 and 3)

AkzoNobel Comment:

(2) historical manufacture and use of peroxides for more than 30 years in the United States has not resulted in respiratory sensitization concerns by U.S. government agencies; (3) worker health assessment does not indicate a respiratory sensitization issue exists for peroxides;

EPA Response:

Disagree. See response to Comment 3.

2.1.3.2 Conclusion (4)

AkzoNobel Comment:

(4) existing engineering controls and PPE ensure that workers will not be exposed to hazardous amounts of the PMN substance;

EPA Response:

In the absence data, EPA must regulate the PMN substance as we would other respiratory sensitizers, such as isocyanate. NIOSH recommends that MDI exposure be limited to 0.05 (mg/m3), so in the absence of data, EPA uses the NIOSH recommendation as the exposure level for respiratory sensitizers. Based on exposure models for this use, EPA expects exposures of higher than 0.05 (mg/m3). Therefore this use may present an unreasonable risk to human health if unmitigated by engineering controls that would reduce exposure to below the NIOSH recommendation or an air supplied respirator. EPA has recommended an air supplied breathing respirator in order to the potential for unreasonable risk during spray operations of respiratory sensitizers. This is in accordance with the NIOSH recommendation for MDI, "On the basis of these finding, NIOSH concludes that only a full-facepiece, supplied-air respirator provides the necessary protection during MDI spray operations".

2.1.3.3 Conclusion (5)

AkzoNobel Comment:

(5) we do not know what EPA's definition of respiratory sensitizer is;

EPA Response:

EPA considers respiratory sensitization to be due to an immunological mechanism that will require more than one exposure to be expressed.

2.1.3.4 Conclusion (6)

AkzoNobel Comment:

(6) the sensitization process in skin is different from that in the respiratory system;

EPA Response:

Agree. Agree in principle that the specific process of respiratory sensitization is different from skin sensitization. However, both are allergic responses to an immune challenge. They both serve in the body's defense against attack by foreign bodies. There is no reason why one form of response would preclude the other.

[redacted]

2.1.3.5 Conclusion (7)

AkzoNobel Comment:

(7) a classification of respiratory sensitization should not be based on the results of one animal laboratory sensitization skin study;

EPA Response:

EPA is not classifying the PMN as a respiratory sensitizer. EPA concludes that the PMN is positive in a skin sensitization study. Because the PMN can cause a response in the immune system from dermal exposure, there is a possibility that it could also cause respiratory sensitization. There is concern that previous dermal exposure can prime the immune system for sensitization via the inhalation route. If the PMN has even poor absorption, then it has the potential to be a dermal and respiratory sensitizer in humans. The guinea pig is the most accurate model for sensitization. In the absence of data, EPA has insufficient information" to state whether or not this chemical is a respiratory sensitizer. In order to mitigate the potential for unreasonable risk, EPA requires further exposure controls and /or personal protective equipment.

2.1.3.6 Conclusion (8)

AkzoNobel Comment:

(8) the results of the one, older skin sensitization study on the PMN chemical are only marginally positive;

EPA Response:

EPA only has the one dermal sensitization study to make a determination. The positive result of the study introduces uncertainty about the potential of the PMN to cause respiratory sensitization.

2.1.3.1 Conclusion (9)

AkzoNobel Comment:

(9) a technically-based Weight-of-Evidence (WoE) approach for respiratory sensitization is appropriate for the PMN chemical; and

EPA Response:

EPA has not concluded that the PMN is a respiratory sensitizer. The PMN is positive in the Guinea Pig maximization test, the most reliable assay relative to humans. As noted in ECHA (2017), a skin sensitizer has the potential to also induce respiratory sensitization. Both skin and respiratory sensitization are allergic responses to an immune challenge. They both serve in the body's defense against attack by foreign bodies. There is no reason why one form of response would preclude the other. EPA is not classifying the PMN as a respiratory sensitizer. EPA concludes that the PMN is positive in a skin sensitization study. Because the PMN can cause a response in the immune system from dermal exposure, there is a possibility that it could also cause respiratory sensitization. Prior dermal exposure may prime the lungs for a respiratory sensitization. In the absence of data, EPA has insufficient information" to state whether or not this chemical is a respiratory sensitizer. In order to mitigate the potential for unreasonable risk, EPA requires further exposure controls and /or personal protective equipment.

[redacted]

2.1.3.2 Conclusion (10)

AkzoNobel Comment:

(10) based on previously submitted peroxide studies EPA should not have a concern for oncogenicity of the PMN substance.

EPA Response:

EPA is not making a "may present and unreasonable risk" finding for carcinogenicity. As noted in the SAT report, the concern level for oncogenicity was marginal. The potential for carcinogenicity due to free radical formation will be a function of the stability of the peroxide and the route of exposure. If a peroxide is too unstable it will degrade before reaching the cells and DNA/macromolecule. There are no data on the PMN to make that determination. However, there is some evidence that a close analog, di-t-butyl peroxide, may induce lymphoma in mice after subcutaneous injection (Lai et al., 1996). Since the subcutaneous injection is unlikely for industrial uses and the study was done in 1960s, a "marginal" concern is considered reasonable.

2.2 Detailed Comments and Questions

2.2.1 Comment 1

AkzoNobel Comment:

(1) There are no data on the PMN chemical that indicate it should be considered a respiratory sensitizer

QUESTION: does the EPA have any published or unpublished data on the PMN substance or structural analogs that would indicate the PMN substance is a respiratory sensitizer?

EPA Response:

EPA does not have any published or unpublished data on the PMN to indicate the PMN is a respiratory sensitizer. However, as noted in the response to Section 2.1.3.1 - The PMN is positive in the Guinea Pig maximization test. As noted in ECHA (2017) above, a skin sensitizer has the potential to also induce respiratory sensitization. In the absence of data, EPA has insufficient information" to state whether or not this chemical is a respiratory sensitizer.

2.2.2 Comment 2

AkzoNobel Comment:

(2) Historical manufacture and use of peroxides has not resulted in respiratory sensitization concerns by U.S. government agencies

QUESTION: Does the Agency have specific new human data that have led it to draw the conclusion that the new peroxide is a respiratory sensitizer? If so, we would like to review the specific new information (e.g., new human data, the results of QSAR modeling, etc.).

EPA Response:

EPA does not have any "specific new human data" to conclude that the PMN would be a respiratory sensitizer. The 2017 Version 6 of the ECHA document (ECHA, 2017) page 315 states *"For substances that sensitise via the respiratory tract, there is still uncertainty regarding the exact mechanisms leading to respiratory sensitisation. Based on the current knowledge the induction of respiratory sensitisation can occur via inhalation or dermal exposure to the sensitising substance (Redlich, 2010; Kimber et al.,*

[redacted]

2015).” The PMN is positive in the Guinea Pig maximization test. As noted in ECHA (2017), a skin sensitizer has the potential to also induce respiratory sensitization. Both skin and respiratory sensitization are allergic responses to an immune challenge. They both serve in the body’s defense against attack by foreign bodies. There is no reason why one form of response would preclude the other. EPA is not classifying the PMN as a respiratory sensitizer. EPA concludes that the PMN is positive in a skin sensitization study. Because the PMN can cause a response in the immune system from dermal exposure, there is a possibility that it could also cause respiratory sensitization. In the absence of data, EPA has insufficient information” to state whether or not this chemical is a respiratory sensitizer. In order to mitigate the potential for unreasonable risk, EPA requires further exposure controls and /or personal protective equipment.

2.2.3 Comment 3

AkzoNobel Comment:

(3) Worker health assessment does not indicate a respiratory sensitization issue exists for peroxides QUESTION: does the EPA have specific human exposure concerns regarding the new peroxide that would support a conclusion of unreasonable risk?

EPA Response:

The lack of worker complaints does not preclude sensitization issues. The statement is not supported by a systematic epidemiology study, or worker surveillance.

2.2.4 Comment 4

AkzoNobel Comment:

(4) Existing engineering controls and PPE ensure that workers will not be exposed to hazardous amounts of the PMN substance

QUESTION: does EPA agree that workers will be protected if they follow the guidelines that EPA has published for new diisocyanates, and specifically use the 3M-recommended full face piece respirator with organic vapor cartridge specifically recommended by 3M for MEKP?

EPA Response:

The published guideline for diisocyanates recommending a full face piece respirator with organic vapor cartridge is for vapor not mist or spray. MEKP has not been reviewed by the EPA as it was grandfathered in with TSCA. We do not have medical monitoring data to agree or disagree with 3M’s recommendation of the full face respirator.

2.2.5 Comment 5

AkzoNobel Comment:

(5) We do not know what EPA’s definition of respiratory sensitizer is

QUESTION: What is the U.S. EPA definition of a respiratory sensitizer? Has this definition been accepted throughout EPA? Has EPA communicated its definition to the public and regulated community?

EPA Response:

EPA considers respiratory sensitization to be an adverse response due to an immunological mechanism that will require more than one exposure to be expressed.

[redacted]

2.2.6 Comment 6

AkzoNobel Comment:

(6) The sensitization process in skin is different from that in the respiratory system
QUESTION: On what scientific basis is the Agency concluding that the PMN chemical may cause respiratory sensitization because it induces skin sensitization via a different biological mechanism?

EPA Response:

See response in Section 2.2.2.

2.2.7 Comment 7

AkzoNobel Comment:

(7) A classification of respiratory sensitization should not be based on the results of one animal laboratory skin sensitization study
QUESTION: What scientific data have led EPA to conclude the PMN substance is a human respiratory sensitizer based solely on one animal skin sensitization study?

EPA Response:

EPA is not concluding the PMN is a respiratory sensitizer. EPA concludes that the PMN is positive in a skin sensitization study. Because the PMN can cause a response in the immune system from dermal exposure, there is a possibility that it could also cause respiratory sensitization. There is too much uncertainty and lack of data to conclude the PMN does not have the potential to cause respiratory sensitization according to TSCA and the positive guinea pig results. In the absence of data, EPA has insufficient information" to state whether or not this chemical is a respiratory sensitizer. In order to mitigate the potential for unreasonable risk, EPA requires further exposure controls and /or personal protective equipment.

2.2.8 Comment 8

AkzoNobel Comment:

(8) The one, older skin sensitization study result on the PMN chemical is only marginally positive "In the skin sensitization study on the PMN substance (NOTOX project 338704), the peroxide was injected into the skin during preliminary testing: concentrations as low as 2% induced necrosis (cell death) in all animals. In the intradermal injection phase of the main study, all animals showed erythema and signs of necrosis (day 3) and all animal epidermal exposure sites showed erythema (day 10). The first challenge readings on day 24 showed no sensitization response. On day 25, 6 of 10 animals showed skin scaliness with two of those animals also showing minimal skim erythema. At the second challenge on days 31-32, 7 of 10 animals showed skin scaliness with minimal skin erythema scores. Skin irritation and inflammation increase the rate of skin turnover leading to scale formation. It is not surprising that the application of a severely irritating substance caused skin cell turnover and skin scaliness. However, this should not be considered a sign of skin sensitization."
QUESTION: Does EPA agree that the minor skin sensitization responses observed only at second challenge may at least in part be due to the strong irritative effects of the PMN chemical following repeated exposure?

[redacted]

EPA Response:
The challenge was conducted at a site distal to the intradermal injection and with a concentration determined to be non-irritating. Therefore the positive response is a sensitization reaction.

2.2.9 Comment 9

AkzoNobel Comment:

(9) *With respect to the weight of the evidence (WOE), we propose that the following decision tree approach published by the European Chemicals Agency (ECHA, 2015) is reasonable to follow for the PMN peroxide:*

a. *QUESTION 1: Is the substance, based on conclusive data, a skin sensitizer (GHS category 1, 1A or 1B?*
   i. *RESPONSE 1: YES**
b. *QUESTION 2: Is the substance a diisocyanate?*
   i. *RESPONSE 2: NO*
c. *QUESTION 3: Are there any structural alerts (such as acid anhydride, platinum salt, etc.)?*
   i. *RESPONSE 3: NO*
d. *QUESTION 4: Based on expert judgment, are there any other good reasons to suppose a potential respiratory sensitization hazard (e.g., human data, animal data, QSAR, in vitro test methods, etc.)?*
   i. *RESPONSE 4: NO*
e. *CONCLUSION: Do not consider the substance a respiratory sensitizer.*
   i. **Note: we do not consider the one older GPMT test to be conclusive*

Based on the use of this published, technical method, we conclude that the PMN peroxide is not a respiratory sensitizer.

QUESTION: Does EPA agree that the WoE approach presented here is reasonable and takes into account the current state of the knowledge of respiratory sensitization, and if not, what is EPA's WoE approach?

EPA Response:
EPA has not concluded that the PMN is a respiratory sensitizer. The PMN is positive in the Guinea Pig maximization test. As noted in ECHA (2017), a skin sensitizer has the potential to also induce respiratory sensitization. Both skin and respiratory sensitization are allergic responses to an immune challenge. They both serve in the body's defense against attack by foreign bodies. There is no reason why one form of response would preclude the other. EPA is not classifying the PMN as a respiratory sensitizer. EPA concludes that the PMN is positive in a skin sensitization study. Because the PMN can cause a response in the immune system from dermal exposure, there is a possibility that it could also cause respiratory sensitization. In the absence of data, EPA has insufficient information" to state whether or not this chemical is a respiratory sensitizer. In order to mitigate the potential for unreasonable risk, EPA requires further exposure controls and /or personal protective equipment.

2.2.10 Comment 10

AkzoNobel Comment:

(10) *We note that the EPA review document sent from Ernest Falke to Gloria Odusote dated September 14, 2018 includes a brief summary of the SAT assessment for mutagenicity and carcinogenicity. The summary mentions a marginal concern for oncogenicity based on potential free radical formation. We would like to remind EPA staff that the issue of the potential oncogenicity of organic peroxides was addressed many years by the Organic Peroxide Producers*

[redacted]

Safety Division (OPPSD). in consultation with EPA, the OPPSD commissioned Dr. Thomas Slaga (University of Texas) to perform a series of in vivo studies in Sencar mice to address this specific issue (Slaga, 2004 NOTE BY EPA-THIS IS REALLY Hanausek et al., 2004*). The results of Dr. Slaga's work showed that organic peroxides should not be considered oncogenic. This work was submitted to EPA and was published in the scientific literature. EPA agreed with the conclusion of the Slaga work and removed organic peroxides from the list of substances potentially thought to be oncogenic. The current chapter for peroxides in the U.S. EPA "TSCA New Chemicals Program (NCP) Chemicals Categories document (downloaded July 24, 2017 from the U.S. EPA website) states, "EPA has reviewed test data developed by the Society of the Plastics Industry (SPI) and others on the peroxide category of chemicals and concludes that available information does not support continued identification of peroxides as a new chemical category presenting concerns for possible carcinogenicity".*

QUESTION: With no new information or rationale, why does EPA still have a concern for oncogenicity and include carcinogenicity in its SAT assessment of peroxides?

EPA Response:

EPA is not making a "may present an unreasonable risk" finding for carcinogenicity. As noted in the SAT report the, the concern level for oncogenicity was marginal. The potential for carcinogenicity due to free radical formation will be a function of the stability of the peroxide and the route of exposure. If a peroxide is too unstable it will degrade before reaching the cells and DNA/macromolecule. There are no data on the PMN to make that determination. However, there is some evidence that a close analog, di-t-butyl peroxide, may induce lymphoma in mice after subcutaneous injection (Lai et al., 1996). Since the subcutaneous injection is unlikely for industrial uses and the study was done in 1960s, a "marginal" concern is considered reasonable.

[redacted]

3 REFERENCES

ECHA. European Chemicals Agency. 2015. Guidance on information requirements and chemical safety assessment. Chapter R.7a: Endpoint specific guidance. Draft version 5.0 July, 2015.

ECHA. European Chemicals Agency. 2017. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance Version 6.0 July 2017.

Hanausek M, Walaszek Z, Viaje A, LaBate M, Spears E, Farrell, Henrich R, Tveit Ann, Walborg E F and Thomas J.Slaga. 2004. Exposure of mouse skin to organic peroxides: sub-chronic effects related to carcinogenic potential Carcinogenesis 25(3):431-7. 2004.

Kimber I, Dearman RJ, Basketter DA and Boverhof DR. 2015. Chemical respiratory allergy: reverse engineering an adverse outcome pathway. Toxicology 318:32-9.

Lai DY, Woo, YT,, Argus, MF and Arcos JC (1996) Carcinogenic potential of organic peroxides: prediction based on structure-activity relationships (SAR) and mechansim-based short-term test. J. Environ. Sci. Heatlh, Vol. C14, 63-80.

Redlich CA. 2010. Skin Exposure and Asthma: Is There a Connection? Proc Am Thorac Soc 7:134–7.

Slaga, t. et. al. 2004 – Note, this is really Hanausek et al.. It was cited incorrectly in Akzo Nobel letter.

USEPA. 2010. TSCA New Chemical Program (NCP) Chemical Categories. U.S. Environmental Protection Agency. Last revised: August, 2010. Downloaded from USEPA website July 24, 2017.